REMARKS

Applicants have cancelled Claims 48 and 49, without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claims 40-45 to delete reference to an extracellular domain. Applicants have also amended Claims 40-44, and 51 to include a functional limitation for the polypeptides. Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. For example, support for the amended claims can be found in the specification at page 142, line 20 through page 143, line 14, for example.

Accordingly, Claims 40-47, and 50-52 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed April 27, 2004. For the reasons set forth below, Applicants respectfully traverse.

Use of Trademarks in the Specification

Paragraphs in the specification containing non-capitalized trademarks have been amended. Accordingly, the trademarks in the specification are now both capitalized and accompanied by the appropriate generic terminology. These amendments to the specification do not add new matter and Applicants respectfully submit that the use of trademarks in the specification is in accordance with MPEP §608.01(v).

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 40-52 under 35 U.S.C. § 101 as lacking patentable utility. More specifically, the PTO alleges that the invention lacks any apparent or disclosed, specific and substantial, credible utility. Applicants respectfully disagree.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, *emphasis* added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. §2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d

1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Specific, Substantial, and Credible Utility

The PTO asserts that the invention allegedly lacks substantial utility because the claims are drawn to polypeptides that have, as of yet, undetermined function or biological significance. More specifically, the PTO argues that evidence in the specification that the claimed polypeptides are capable of inducing the expression of c-fos in pericyte cells, is not sufficient to adequately support the asserted utilities of diagnosing and treating tumors, and stimulating angiogenesis under 35 U.S.C. §101.

Applicants respectfully disagree. While 35 U.S.C §101 only requires that one specific, substantial, and credible utility be either asserted or well established, the specification provides at least three asserted utilities for the claimed polypeptides. The first two disclosed utilities are that the claimed polypeptides induce the expression of c-fos in pericyte cells, and therefore, are useful not only as diagnostic markers for pericyte associated tumors, but also for giving rise to antagonists (*e.g.*, antibodies) that are useful for the therapeutic treatment of pericyte associated tumors. Thus the first two disclosed utilities relate to pericyte tumor diagnosis and treatment. Furthermore, as c-fos expression induces angiogenesis, the third asserted utility is that the

claimed polypeptides are useful in stimulating angiogenesis. Inducing angiogenesis could be beneficial for patients in need of wound healing, for example.

As the assertion of a utility creates a presumption of utility sufficient to satisfy 35 U.S.C. §101, the burden is on the Examiner to prove that it is more likely than not that a skilled artisan would doubt the truth of the statement of utility. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

The PTO has attempted to rebut the presumption of utility by relying on three references to support its position that c-fos expression represents a general cellular response to a variety of stimuli. According to these cited references, alleged stimuli capable of inducing c-fos include growth factors, cytokines, serum, UV-light, neurotropic factors, neurotransmitters, depolarizing agents, and ion channel activating agents. The PTO concludes that because "c-fos appears to be a non-specific first line of cellular response, one skilled in the art would readily conclude that activation of c-fos could not support the assertion of specific and substantial credible utility of PRO444 'as diagnostic marker[s] for particular types of pericyte-associated tumors'."

Applicants respectfully disagree with the PTO's position. The PTO appears to be asserting that because numerous stimuli are capable of inducing c-fos, the expression of c-fos is a non-specific first line of cellular response, and therefore not a sufficiently asserted utility. Contrary to the PTO's stated position, the important issue to consider is not whether numerous stimuli are capable of inducing the expression of c-fos, but rather, whether the ability to induce c-fos, by itself, is a substantial, specific and credible utility sufficient to satisfy the requirements of 35 U.S.C. §101.

In addressing the above-stated issue, Applicants respectfully submit that polypeptides capable of inducing c-fos expression have a substantial, specific, and credible use. More specifically, the c-fos gene is a well known proto-oncogene that is a major target for signal transduction pathways involved in the regulation of cell growth, differentiation, and

transformation. (*See*: Saez *et al.*, "c-fos is required for malignant progression of skin tumors" *Cell*, 82(5) 721-32, Sept. 8, 1995 submitted herewith). In a study that examined whether c-fos deficient mice were capable of developing cancer, it was shown that mice containing a c-fos knockout gene failed to develop malignant tumors, whereas wild-type mice (c-fos positive) did. (*Id.*) The authors of the study concluded that c-fos deficient cells appear to have an intrinsic defect that hinders tumorgenesis. (*Id.*)

In light of the above study, one skilled in the art would reasonably conclude that the claimed polypeptides have real world utility. More particularly, these polypeptides (PRO444) induce the expression of a transcription factor (c-fos) described as critical in tumorgenesis. Thus, the presence of the claimed polypeptides in a subject's tissues or cells (*e.g.,* pericytes) would indicate that the c-fos proto-oncogene is expressing more c-fos transcription factor than normal, and it is more likely than not that the patient has a malignant tumor. Similarly, as c-fos transcription factor has been suggested to be critical in tumorgenesis, the absence of the claimed polypeptides in a subject's tissues or cells (*e.g.,* pericytes) would indicate that it less likely than not that the patient has a malignant tumor.

With respect to the second asserted utility, the claimed polypeptides could also be useful in generating antibodies (*e.g.,* monoclonal antibodies) against PRO444, using techniques that are well known in the art. Specific techniques for generating anti-PRO antibodies are described in detail in the specification. For example, pages 91-92 of the specification describe how a skilled artisan can readily generate anti-PRO444 monoclonal antibodies. These generated antibodies would have a neutralizing effect on PRO444's functional activity. Furthermore, a skilled artisan would reasonably conclude that a reduction in PRO444 activity would, in turn, minimize the expression of c-fos proto-oncogene, and thus could be used in a treatment regimen for a patient suffering from a malignant tumor. As stated above, c-fos has been suggested to be a critical factor in the onset of tumorgenesis. Accordingly, even if other stimuli are capable of inducing c-fos expression in the patient, it would still be beneficial to prevent the expression of a proto-oncogene suggested to be necessary for tumorgenesis to any extent possible. Thus, the fact that other stimuli have been reported to induce c-fos, is not dispositive of the issue. In light of their

ability to generate PRO444 antibodies, the claimed polypeptides possess specific, substantial and credible therapeutic benefits for cancer patients.

Applicants also wish to address the third asserted use of the claimed polypeptides, which relates to their ability to induce angiogenesis, or the formation of new blood vessels. More specifically, it is well established that c-fos is capable of inducing growth factors that induce the onset of angiogenesis. (*See*: Marconcini *et al.*, "c-fos induced growth factor/vascular endothelial growth factor induces angiogenesis in vivo and in vitro" *Proc. Natl. Acad. Sci. U.S.A*, 96(17): 9671-6, Aug. 17, 1999 submitted herewith). Accordingly, the claimed polypeptides could be administered to a patient in need of angiogenesis. As discussed in the specification, angiogenesis is useful in facilitating wound healing in a patient. More specifically, the generation of new vessels provide nutrients to the wound site, promote granulation tissue formation, and facilitate the clearance of debris. Again, it is important to reiterate that the claimed polypeptides are helpful in stimulating angiogenesis, regardless of whether or not other compounds have been reported to stimulate angiogenesis or c-fos induction.

The PTO also argued that the disclosed utilities were not specific enough because the specification fails to identify "a particular type of tumor that the PRO444 is specifically associated with." However, this is not the standard for determining whether a "specific" utility has been asserted. Applicants statements as to the claimed polypeptides usefulness in treating and diagnosing pericyte-associated tumors, are sufficiently specific to satisfy the requirements of 35 U.S.C. §101. Cancer is an extensively studied and well known physiological condition that is readily characterized by its numerous specific properties. Applicants are not required to recite exact tumor types (e.g., breast, brain) that the claimed inventions can treat or diagnose in order to comply with the PTO's utility requirements. There are numerous general treatments (e.g., radiation, chemotherapy) and diagnostics available for cancer that are not limited to exact types of cancer, yet have well established specific utility. Applicants also note that stimulating angiogenesis is a sufficiently specific asserted utility of the claimed polypeptides. For these reasons, Applicants assert that the claimed inventions have sufficiently "specific" utility.

Lastly, Applicants emphasize that 35 U.S.C. §101 only requires the application to have *one* asserted "specific, substantial, and credible utility" or a "well-established utility." *See* Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001). Accordingly, if the Examiner finds that the claimed polypeptides have substantial, specific and credible utility in any of the three utilities asserted and discussed herein (*e.g.,* treating or diagnosing tumors, or stimulating angiogenesis), this rejection must be withdrawn.

Conclusion

Applicants have provided arguments and references to show that the claimed invention does have specific, substantial, and credible utility. Applicants submit that one of ordinary skill in the art would have no legitimate basis to doubt the credibility of the statements made in the specification and herein that set forth the expressly stated utilities of the claimed polypeptides.

Thus, given the totality of the evidence provided, Applicants submit that they have established a specific and substantial, credible utility for the claimed polypeptides either as diagnostic or therapeutic agents associated with cancer, or for stimulating angiogenesis. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific and substantial credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112 – Enablement

The PTO also rejected Claims 40-52 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the PTO tied this rejection to the 35 U.S.C. §101 rejection, set forth above, and argued that since the claimed invention is not supported by either a clear asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

The Applicants respectfully assert that the arguments set forth in detail above make clear that the claimed polypeptides are useful in diagnosing and treating cancer, and inducing angiogenesis in a subject in need. In light of PRO444's demonstrated ability to stimulate c-fos expression, each of the asserted utilities is specific, substantial, and credible. Accordingly, the specification teaches a sufficient utility such that a skilled artisan could make and use the claimed inventions without undue experimentation. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112 – Written Description

The PTO rejected Claims 40-44, 51 and 52 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the PTO alleged that Claims 40-44, directed to polypeptides having at least 80%, 85%, 90%, 95%, or 99% sequence identity with a polypeptide of SEQ ID NO: 9, and Claims 51 and 52, directed to chimeric polypeptides, claim too broad of a genus. The PTO further alleged that there was no written description in the specification that provided any distinguishing features of the claimed polypeptide sequences.

Applicants respectfully disagree. In light of the detailed specification regarding polypeptide sequence identity, and chimeric polypeptides, those with skill in the art would readily understand that Applicants had possession of the claimed polypeptides. *See* Specification page 33, lines 4-20, page 40, lines 3-8, page 75, lines 33-37, and page 76, lines 1-3.

However, in order to advance the present case towards allowance, Applicants have amended Claims 40-44, and 51 to show possession of the claimed polypeptides by providing corresponding functional limitations. More particularly, Claims 40-44, 51, and 52 now encompass polypeptides having the ability to induce c-fos expression. As disclosed in detail in Example 60 of specification (pages 142-143), polypeptides having the ability to induce c-fos proto-oncogene expression, were clearly possessed by Applicants at the time of filing the present

application. In view of the current status of the claims, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §112 – Definiteness

Claims 40-52 were rejected under 35 U.S.C §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More specifically, Claims 40-45, 48, and 49 were alleged to be vague and indefinite for the recitation of the term "extracellular domain." These claims have either been amended to no longer recite this term or cancelled. Accordingly, Applicants respectfully request the PTO to reconsider and withdraw this rejection.

Finally, the PTO rejected Claims 46, 47, 50, and 51 for being dependent on the above claims. As the above claims have either been amended to resolve any issue regarding indefiniteness, or cancelled, Applicants respectfully submit that Claims 46, 47, 50, and 51 are also definite. Accordingly, it is respectfully requested that PTO reconsider and withdraw all indefinite rejections of the pending claims.

CONCLUSION

In view of the above, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 26, 2004

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